BIOCHEMISTRY LECTURES BY

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ADDITIONAL NOTES ON DIGESTION AND ABSORPTION OF SUGARS

- The problem of flatulence after ingestion of leguminous seeds (Beans, peas and soya) is caused by higher oligosaccharides (raffinose and stachyose) that cannot be hydrolysed by human intestinal enzymes

- Glucose has specific transporters which are trans-membrane proteins. They include:

- Sodium dependent glucose transporter 1 (SGLUT- 1) in the small intestine mediates the transport of glucose from the lumen into the intestinal epithelial cells. It carries glucose along with sodium, hence it is a co-transporter.

ADDITIONAL NOTES ON DIGESTION AND ABSORPTION OF SUGARS

- GLUT-2 (glucose transporter -2) of the small intestine is a uniport system that transports glucose from the intestinal epithelial cells into the bloodstream and it is independent on sodium.

- GLUT-1 found in erythrocytes, kidney, retina, placenta, brain mediates glucose uptake in the cells.

- GLUT-4 (found in adipose tissues, heart and skeletal muscles) is insulin sensitive i.e it is under the control of insulin. Other glucose transporters are not under the control of insulin. Insulin induces GLUT-4 molecules and thus increases glucose uptake by cells.

LECTURE 2 : OUTLINE

- USE OF ENZYMES IN DIAGNOSIS
- ISOENZYMES
- BLOOD CLOTTING AND ENZYMES

USE OF ENZYMES IN DIAGNOSIS

- Plasma contains many **functional enzymes** which are actively secreted into plasma. E.g, enzymes of blood coagulation

- There are also few **non- functional enzymes** in plasma which are released from cells of various tissues due to damage.

USE OF ENZYMES IN DIAGNOSIS

- The normal plasma levels of these non-functional enzymes are low but are drastically increased during cell death (necrosis), damage or disease because they are released from the damaged tissue that contains it. The plasma activity of the enzymes falls when the injury subsides.

- Therefore, assays of these enzymes in plasma are very useful in diagnosis of diseases, associated with the tissues that produce them

ISOENZYMES

- Isoenzymes or isozymes are physically distinct forms of the same enzyme activity. They are enzymes that differ in amino acid sequence but catalyze the same reaction

- Different forms of a particular enzymes can be found in various tissues. For example, Lactate dehydrogenase (LDH) has five isoenzymes. LDH has H and M subunits which combine in different forms depending on the tissue in which it is present as shown below:

TABLE 1: LDH ISOENZYMES

TYPE	COMPOSITION	LOCATION
LDH1	HHHH	HEART AND ERYTHROCYTE
LDH2	HHHM	HEART AND ERYTHROCYTE
LDH3	HHMM	BRAIN AND KIDNEY
LDH4	HMMM	SKELETAL MUSCLE AND LIVER
LDH5	MMMM	SKELETAL MUSCLE AND LIVER

- Many enzymes are produced by more than one tissue in the body, thus an increase in the plasma level of an enzyme could be a reflection of damage that may not be **confined** to any of such tissues

- However, there are enzymes that are **specific** to some particular tissues , such enzymes are useful in detecting a damage to the tissues involved.

- The determination of a specific isoenzyme form is important in identifying the particular tissue that the enzyme is released from, since different isoenzyme forms are found in various tissues. This is useful in identifying the organ with damage.

ENZYMES USED IN DIAGNOSING HEART DISEASE

The major enzymes used in diagnosing heart diseases are:

- Total creatine kinase (total CK)
- Creatine kinase-MB isoenzyme (CK-MB)
- Aspartate aminotransferase (AST) also known as serum glutamate oxaloacetate transaminase (SGOT)
- Lactate dehydrogenase (LDH)

ENZYMES USED IN DIAGNOSING HEART DISEASE

- **CK-MB and LDH** are the **most specific** enzymes for myocardial infarction. **Total CK** elevation is not specific to the heart, as it may be derived from the heart or skeletal muscle (CK-MM).

- Thus, the finding of high CK-MB along with an elevated total Ck does not exclude myocardial damage as a cause of the high levels of total CK.

LIVER FUNCTION TESTS

Certain enzymes are measured in the serum to assess liver function, detect liver diseases or injury. They include the following:

- Aspartate aminotransferase (AST) also known as serum glutamate oxaloacetate transaminase (SGOT)
- Alanine aminotransferase (ALT) also known as serum glutamate pyruvate transaminase (SGPT)
- Alkaline phosphatase (ALP)
- Gamma Glutamine Transpeptidase (GGT)
- 5‘ Nucleotidase

LIVER FUNCTION TESTS

- AST is a sensitive index of active damage of hepatocytes, it is useful in detecting the onset of early hepatitis or latent liver cell damage

- An increase in ALP level of above five fold its upper reference point is suggestive of **cholestasis** (A suppression of the flow of bile caused by an obstruction associated with the liver)

- GGT is particularly useful for detection of cholestasis in liver disease

- 5‘ Nucleotidase is specific for detecting hepatobiliary obstruction.

BONE DISEASE ENZYMES

- The enzyme commonly measured in bone disease is ALP because it is secreted by osteoblasts.

- The highest rises of ALP (more than ten times the upper reference range) occurs in Paget's disease of the bones, osteomalacia and rickets

- Note that : ALP level is higher than normal in childhood and in pregnancy as physiological conditions rather than disease conditions.

MUSCULAR DISEASES ENZYMES

- Creatine kinase (CK) is the most commonly measured, most reliable and sensitive biochemical index of muscle disease.

- AST and Fructose 1,6-Bisphosphate aldolase are also useful indices but are less sensitive.

- Isoenzyme assay of Creatine kinase (CK-MM) is usually preferred to the total CK assay, for greater specificity.

ENZYMES USED IN DIAGNOSING PROSTATE CANCER

- **Acid phosphatase (ACP)** is useful in the diagnosis of prostate cancer and to monitor its treatment

- The use of **prostate specific antigen (PSA)** is now the preferred biochemical diagnostic assay for prostate cancer .

BLOOD CLOTTING AND ENZYMES

- The biochemical mechanism of blood clotting is a typical example of **cascade activation**.

- The blood clotting factors are present in circulation as inactive zymogens. They are converted to their active forms only when the clotting process is initiated. The aim of this is to prevent unnecessary intravascular blood coagulation.

ROLE OF CALCIUM AND VITAMIN K IN BLOOD CLOTTING

- Several of the blood clotting factors require calcium for their activation. The calcium ions are chelated by the gamma carboxyl group of glutamic acid residues of the factors II, VII, IX, X XI and XII.

- Vitamin K is required for complete synthesis of blood clotting factors. The gamma carboxylation of glutamic acid residues is dependent on vitamin K.

- Without vitamin K, blood clotting is seriously impaired and uncontrolled bleeding occurs.

PATHWAYS OF BLOOD CLOTTING

(A) EXTRINSIC PATHWAY

- Coagulation is initiated by factor III or tissue factor following an injury to the endothelium of the blood vessels.
- Factor VII binds to tissue factor in the presence of Calcium ions and the resulting complex initiates the blood clotting process as well as the activation of factor X.
- The complex formed from activated factor X and factor V catalyzes the cleavage of thrombin from prothrombin.
- The thrombin formed now catalyzes the activation of factor V, VII,VII and XIII as well as the formation of fibrin from fibrinogen

INTRINSIC PATHWAY

- On injury to the endothelial lining of blood vessels there is a contact activation of factor XII, the autocatalytic action between factor XII and kalleikren to give activated factor XII which in turn activates factor XI.

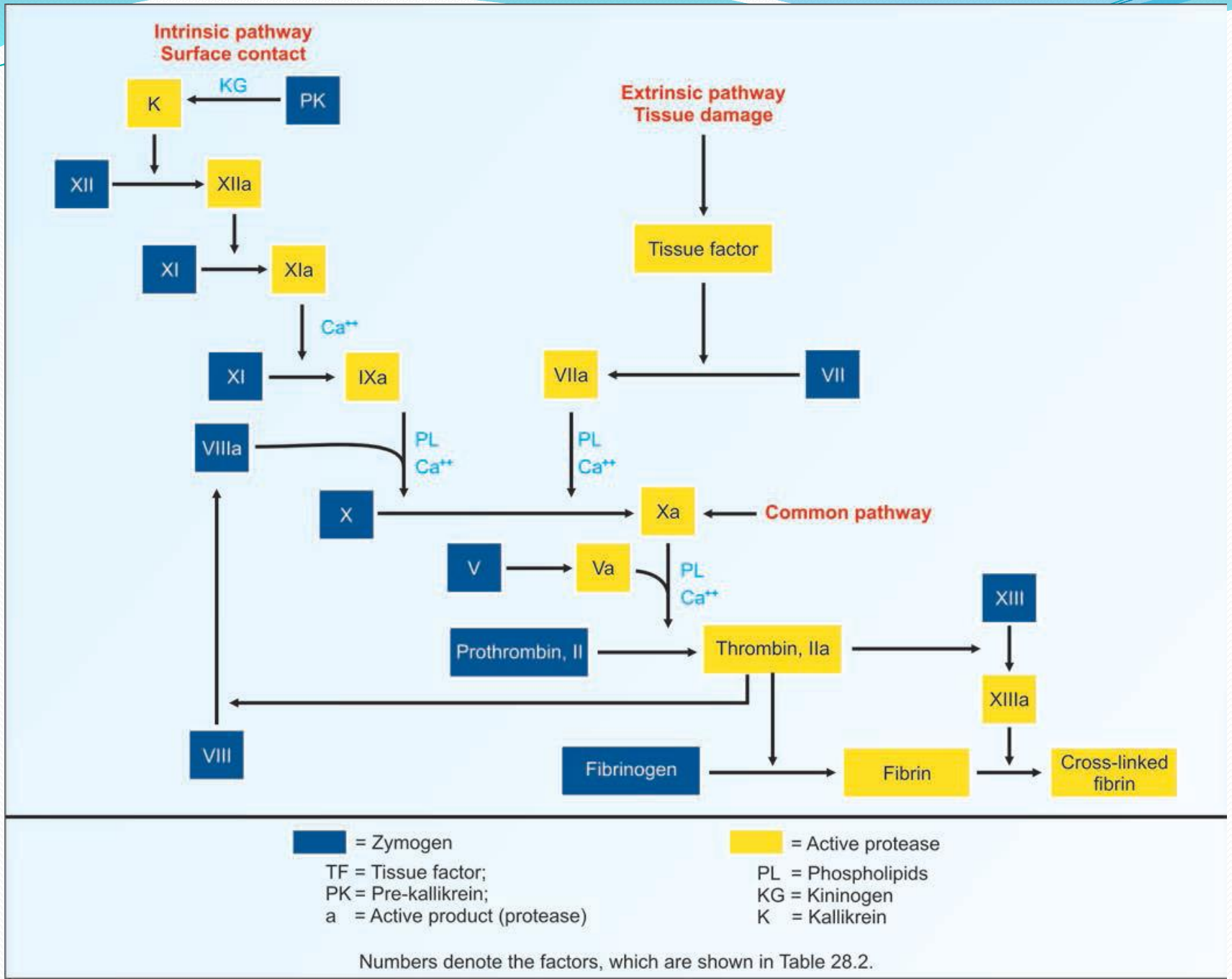
- Activated factor XI activates factor IX which in the presence of factor VIIIa (factor VIII requires thrombin for activation) activates the clotting process. Factor IXa activates factor X

- Activated factor X in the presence of active Factor V as a cofactor catalyzes the activation of prothrombin to produce thrombin.

- The thrombin formed catalyzes the formation of fibrin from fibrinogen. Active factor XIII actively forms a hard clot by catalyzing the formation of cross-links between fibrin monomers of the soft clot.

- The final common route for both the intrinsic and extrinsic pathways involves the activation of prothrombin to thrombin by factor Xa in the presence of factor V.

- It also includes the conversion of fibrinogen to fibrin by thrombin, as well as the cross-linking of fibrin monomers by factor XIIIa


Intrinsic pathway
Surface contact
KG
K
PK
XII
XIIa
XI
XIa
Ca++
XI
IXa
VIIIa
PL
Ca++
X
Extrinsic pathway
Tissue damage
Tissue factor
VIIa
VII
PL
Ca++
Xa
Common pathway
V
Va
PL
Ca++
Prothrombin, II
Thrombin, IIa
XIII
XIIIa
VIII
Fibrinogen
Fibrin
Cross-linked fibrin
= Zymogen
= Active protease
TF = Tissue factor;
PK = Pre-kallikrein;
a = Active product (protease)
PL = Phospholipids
KG = Kininogen
K = Kallikrein
Numbers denote the factors, which are shown in Table 28.2.

HEMOPHILIA

- Hemophilia is an inherited disorder of the clotting system that results in bleeding.

- The deficiency of factor VIII causes hemophilia A , an X Chromosome linked disease, which affects mostly males.

- Hemophilia B is due to the deficiency of factor IX, its clinical features are identical to those of hemophilia A.